National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Cannabidiol for adjuvant treatment of seizures associated with Dravet syndrome or Lennox-Gastaut syndrome

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment: the draft remit

Section	Consultee/ Commentator	Comments	Action
Timing Issues	GW Research Ltd	No Current treatment options for many patients with LGS and DS who are inadequate controlled on currently available anti-epileptic drugs.	Comment noted.

Comment: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	GW Research Ltd	Death during childhood is common in DS. Sudden unexpected death in epilepsy (SUDEP) and Status Epilepticus (SE) are the most common causes of death in DS, with drowning and accidental death following seizures also common causes. Risk factors for SUDEP include frequent generalized tonic–clonic seizures, early seizure onset, polytherapy, and developmental delay (Sillanpää, 2010), all of which are common in DS. A recent review of 177	Comment noted. The background section is intended as a brief overview of the disease area, therefore no

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		unique cases of death in DS reported in the literature highlighted that 73% of the deaths occurred before the patient reached 10 years of age, with the cause being SUDEP in 49% of cases, and SE in 32% of cases (Shmuely, 2016). Longitudinal follow-up (median 17 years) of 100 unrelated DS patients enrolled into the Epilepsy Genetics Research Program reported 17 deaths with a median patient age of 7 years, equating to a DS specific mortality rate of 15.84 per 1000 patient years (Cooper, 2016). SUDEP was the most common cause of death (59%), equating to a DS-specific SUDEP rate of 9.32 per 1000 patient years, which is nearly twice the rate for adults with refractory epilepsy. Cooper MS, Mcintosh A, Crompton DE, Schneider A, McMahon JM, Schneider A et al. Mortality in Dravet syndrome. Epilepsy Res. 2016; 128:43-47. Shmuely S (2016) Mortality in Dravet syndrome: A review Epilepsy and Behaviour. Epilepsy & Behavior 64, 69–¬74 Sillanpää and Shinnar, Long-term Mortality in Childhood-Onset Epilepsy. N Engl J Med 2010; 363:2522-2529	amendments required.
The technology/ intervention	GW Research Ltd	The precise mechanisms by which cannabidiol exerts its anticonvulsant effects in humans are unknown. Cannabidiol reduces neuronal hyperexcitability and inflammation through modulation of intracellular calcium via GPR55 and TRPV1 channels and modulation of adenosine-mediated	Comment noted. The scope has been amended to reflect the expected mechanism of

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<tr><th>Section</th><th>Consultee/ Commentator</th><th>Comments</th><th>Action</th></tr>
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<tr><td>Population</td><td>GW Research Ltd</td><td>LGS accounts for 1 to 4% of childhood epilepsies, and 10% of epilepsies starting in children under the age of 5 years.
LGS prevalence has been estimated at 0.9 per 10,000 population of all ages, and an incidence of 2 new cases per 100,000 children aged 0 to 14 years per year.

Extrapolating statistics for the United Kingdom from the Office for National Statistics in 2016[ONS 2016], we can calculate that the likely number of patients with LGS will be as shown in Table below;

<table>
<tr><td></td><td>England</td></tr>
<tr><td>Total population 2016</td><td>55,268,100</td></tr>
<tr><td>Population aged 0-14 years 2016</td><td>9,927,600</td></tr>
<tr><td>Prevalence of LGS</td><td>4,974</td></tr>
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</td><td>Comment noted.</td></tr>
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Section	Consultee/ Commentator	Comments	Action
		Incidence in children aged 0-14 years: 199	
Outcomes	GW Research Ltd	Include in the outcome measures; change in drop seizures (defined as tonic-clonic, tonic or atonic seizures that led, or could have led, to a fall or injury). Care Giver Impression of Change measuring improvement in patient's quality of life from the care giver and/or physician perspective is relevant in this case due to the lack of developmental progression in the majority of these patients.	Comment noted. At the scoping workshop it was noted that 'change in drop seizures' would be captured by the outcome 'seizure frequency (by seizure type)'. Care giver-related quality could be considered under health-related quality of life or could be captured within the innovation section.
Other	Association of	Important to ensure adults with these conditions are included in the scoping	Comment noted.

Section	Consultee/ Commentator	Comments	Action
considerations	British Neurologists	workshop Important to ensure if the agent is taken forward for further consideration, barriers to access do not become onerous, as is currently the case (for example) for stiripentol use in adults with Dravet Syndrome (with particular current difficulties when children on the drug reach the age of 18, for example, or if stiripentol needs to be started after the age of 18 years, when the condition is the same as it was before the patient's 18th birthday)	Guidance will only be issued in accordance with the marketing authorisation. At the scoping workshop the clinical experts noted that they did not expect any differences in clinical management between adults and children.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health